

# Division of Cardiovascular Medicine



Mark Josephson, MD,  
Chief

## ● *Overview*

The Cardiovascular Division at BIDMC is devoted to providing the highest level of patient care, committed to the unwavering educational mission of academic medicine, and dedicated to state of the art research on the clinical, basic and translational forefronts of cardiovascular disease. The numerous accomplishments of the division are made possible by the outstanding, nationally and internationally recognized faculty, many of whom hold national leadership positions in cardiac epidemiology, basic investigation and clinical trials.

Highly trained, exceptional clinicians care for our patients. Collaborative care utilizing cutting edge technologies, state-of-the-art therapies and common sense patient management is practiced in collaboration with the surgical and medical specialties. Our fellowship program continues to be ranked among the top in the country which is reflected by the quality of candidates that choose to train with us year after year. Cardiovascular research continues to broaden. Some of the current research being conducted includes ischemic heart disease, angiogenesis, heart failure, cardiac arrhythmias, cardiac imaging, preventive cardiology, and cardiac tissue reengineering.

## ● *Clinical Programs*

### *Cardiac Catheterization Laboratory –*

The Interventional Cardiology section continues to be one of the most clinically active groups in the state, performing 4000 diagnostic and interventional procedures. Over the past year the group has worked collaboratively with the Emergency Department to reduce our response time for treatment of patients with acute myocardial infarction to where it is one of the top in the nation.

The faculty continues to have a national and international reputation for clinical research. In the past year members of the section addressed safety of drug-eluting stenting, by establishing an international consortium working with the FDA to better define this issue and publishing 4 papers and an important editorial in the *New England Journal of Medicine*. Other research efforts have resulted in numerous publications in the last academic year.

### *Cardiac Electrophysiology –*

The members of the Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service have a national and international reputation as pioneers in the understanding of arrhythmia pathophysiology and new techniques for their diagnosis and treatment. The distinguished reputation of our EP program is highlighted by the publication of the 4th edition of Dr. Josephson's definitive text *Clinical Cardiac Electrophysiology* (aka the "Bible" of Electrophysiology). In addition, the electrophysiology faculty published over forty-five manuscripts, chapters, and editorials during the past year. Advanced EP fellows are actively involved in both clinical and basic research in addition to patient care duties. The EP service provides the entire spectrum of diagnostic and ablative therapies, including those for AF and VT/VF, as well as the latest in implantable devices and pacemakers.

The arrhythmia service consists of both inpatient and outpatient consultation service, including a dedicated atrial fibrillation clinic run by Dr. Peter Zimetbaum. The Nonlinear dynamics laboratory, directed by Dr. Ary Goldberger, is a basic science laboratory devoted to signal processing and serves as a unique link. The ECG laboratory is directed by Dr. John Markis, processing over 62,000 electrocardiograms per year. An outpatient monitoring service is directed by Drs. Jack Wylie and Alexi Shvilkin.

### *Cardiovascular Health and Lipid Center*

– The Center is under the direction of Dr. J. Peter Oettgen, and is a multidisciplinary prevention clinic. The major clinical focus of the clinic is to assess and reduce cardiovascular risk. Many patients have complex lipid disorders or hypertension that is not easily managed with standard therapies. The Center is also a forum for clinical research. All clinical information and laboratory results are incorporated into a longitudinal database tracking patient responses to dietary and pharmacological strategies.

*Cardiac MR Center* – The full-time staff was expanded to include two of our recent graduates – Drs. David O’Halloran and Yuchi Han. Clinical volume continues to grow (over 700 studies/year). Research efforts resulted in seminal publications in the areas of MR coronary vein imaging, MR identification of left atrial scar in patients undergoing radiofrequency ablation for atrial fibrillation, and CMR characterization of mitral valve prolapse. In addition, the Center received an RO1 grant to apply CMR methods to characterize aortic plaque and its response to therapy in 420 subjects with metabolic syndrome. Overall, the efforts of the non-invasive group resulted in over 20 peer-reviewed publications and 2 patent submissions. Spearheaded by Dr. Evan Appelbaum, the CMR Core Laboratory at PERFUSE has also continued to grow with nearly 10 trials now underway or completed.

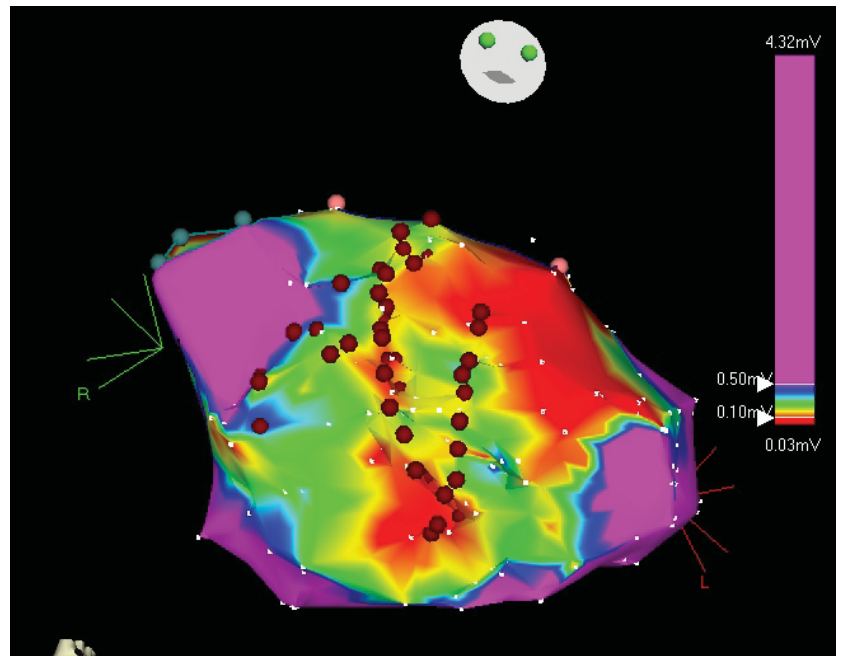
*Exercise Testing/Clinical Physiology* – The laboratories are directed by Drs. Ernest Gervino and Robert Healy. Exercise treadmill, cycle ergometry, and pharmacological testing are employed in this busy laboratory, which performs almost 7,000 tests yearly. Physiological testing is performed in patients with known or suspected coronary artery disease and those at risk for sudden cardiac death. In select populations, metabolic stress testing is performed to assess cardiac function. Testing modalities range from basic ECG and blood pressure monitoring to imaging studies with either nuclear isotopes or echocardiography.

*Heart Disease in Diabetes* – Under the direction of Dr. Donald Cutlip, the Diabetic Heart Clinic has been developed as a joint initiative of BIDMC and the Joslin Clinic.

The aim of this clinic is to offer exceptional and collaborative care to improve outcomes among diabetic patients at high risk for cardiovascular disease as well as those with diabetes and a known history of heart disease.

*Heart Failure* – The multi-disciplinary clinical heart failure program at BIDMC utilizes a growing armamentarium of new preventive and therapeutic approaches for the treatment of patients with mild to severe cardiac dysfunction. Resynchronization therapy to treat heart failure has become a standard at BIDMC. For the critically ill patient, on-site formal cardiac transplantation evaluation is provided as well and the ability to implant ventricular assist devices. Entry and on-site participation in major FDA-approved clinical studies including destination therapy ventricular assist devices and artificial heart programs are currently in development.

*Non-invasive Cardiovascular Imaging* – This past year saw the continued growth of the non-invasive cardiac imaging laboratories both in clinical volume and research activities. All of our readers have passed the American Board of Echocardiography special competency examination in echocardiography. The labora-



• A 3-dimensional electroanatomic map of the left ventricle used to guide catheter-based treatment of ventricular tachycardia, a life-threatening arrhythmia, in a patient with a prior heart attack.

tory received accreditation in transthoracic echocardiography, transesophageal echocardiography, and stress echocardiography by the Intersocietal Commission for the Accreditation of Echocardiography Laboratories (ICAEL). Echo volume in the Echocardiography laboratory continues to grow (over 4%) to nearly 14,500 studies/year with a shift towards increasing outpatient volume and stress echocardiography volume. We also expanded our hours to include Saturday outpatient scanning and have added 3D echocardiographic capability to the already “state of the art” digital lab.

*Nuclear Cardiology* – Under the supervision of Dr. Thomas Hauser, nuclear cardiology is a collaborative effort with the Department of Radiology that provides fellows with the experience necessary to use and interpret a spectrum of cardiac radionuclide exams. One PET/CT unit, six SPECT cameras and two planar cameras are available for cardiac studies, incorporating the most advanced imaging and analysis techniques currently available.

● *Quality Improvement*

Dr. Kalon Ho and Dr. Julian Aroesty have led the Divisional efforts to track indices of quality and improve our performance. They, and other members of the Division, worked closely with colleagues from other departments to improve the quality of cardiovascular care we

deliver. BIDMC continues to be cited by the Centers for Medicare and Medicaid Services as having a risk-adjusted 30 day mortality rate for patients with heart failure that was better than the U.S. national rate. Our risk-adjusted

in-hospital mortality following percutaneous coronary intervention remains better than expected in the National Cardiovascular Data Registry. We have made further improvements

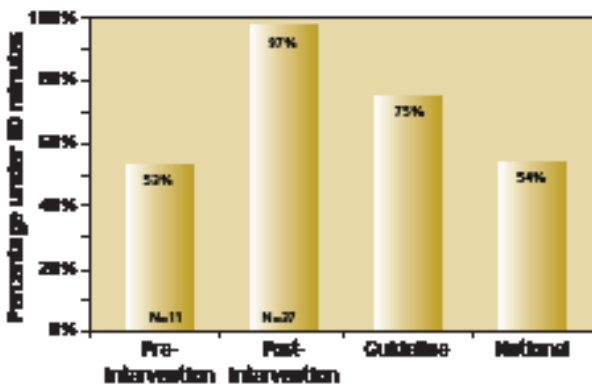
in the timeliness of reperfusion therapy (door-to-balloon time) for patients presenting to the Emergency Department with acute ST segment elevation myocardial infarctions (see figure), and we continue to perform well on Joint Commission core measures of cardiac care.

One of the major initiatives this academic year focused on radiation safety. The Division took the lead in working with the Radiation Safety Committee to improve the informed consent process for patients, with more education about the potential risks of extended fluoroscopic exposures before invasive procedures. We also expanded our divisional continuing medical education activities related to fluoroscopy and implemented a formal radiation safety credentialing process for all attending physicians and fellows who operate fluoroscopic equipment.

Finally, members of the Division remain leaders in state, national and international quality improvement efforts at the Massachusetts Department of Public Health, the National Cardiovascular Data Registry, the American College of Cardiology, the Food and Drug Administration, and the International Guidelines Applied in Practice Door-to-Balloon (D2B) Alliance.

● *Educational Programs*

The educational programs in the Cardiovascular Division have enjoyed significant success this year. Scholarly activity has increased among the fellows, who have garnered prestigious national awards and grants such as the American College of Cardiology, Merck, American Heart Association, Johnson & Johnson Cordis Corporation Fellowship awards. The fellows have presented their work at national meetings and published their work in prestigious journals and books. Dr. William Maisel accepted the position as director of the clinical cardiac electrophysiology fellowship and has made substantial strides in improving the education, recruitment and evaluation of these fellows. Dr. Lawrence Garcia has deftly handled the numerous challenges involved with training high-quality interventional cardiologists in both coronary and peripheral vascular



● Timeliness of reperfusion therapy at BIDMC compared to national guidelines and averages.

intervention. Drs. Eli Gelfand and Duane Pinto have led initiatives in the general cardiology fellowship aimed at improving didactic teaching, evaluation tools and mentorship. Their efforts culminate in the ACGME giving a full 5-year accreditation to all three fellowships and a commendation to the general cardiology



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• Dr. Mark Josephson consults with a patient.

fellowship. Admission to the fellowships remains highly competitive, and high quality individuals from prestigious institutions continue to select our programs. Four individuals from our own internal medicine housestaff program distinguished themselves among over 700 applicants and will be joining the BIDMC general cardiology fellowship in 2009.

Additionally, our faculty continues to actively educate the medical community. This year one of Harvard Medical School's top-ranked education programs was "ECGs in Clinical Practice: Pearls and Pitfalls." Four hundred – a record – attendees from around New England participated. Furthermore, Dr. Josephson and his colleague Dr. Hein Wellens are completing their 27th consecutive year teaching "Understanding Complex Arrhythmias" in the USA and Europe.

### ● *Research Activities*

Over the past two years, Drs. Josephson and Rosenzweig have led efforts to expand and enhance the already strong cardiovascular

### *Research Funding • AY'07*

<b>Federal Direct</b> .....	<b>8,083,613</b>
<b>Federal Indirect</b> .....	<b>3,855,932</b>
<b>Other Direct</b> .....	<b>3,108,943</b>
<b>Other Indirect</b> .....	<b>482,830</b>

research program at BIDMC. This has been implemented through targeted support of particularly exciting research developments, as well as strategic recruitment of five new faculty members, and has culminated in the recently completed move of most of these laboratories to the new Center for Life Sciences (CLS) Building. This building provides an ideal, multi-disciplinary environment in which the cardiovascular research programs can flourish. Of particular note are new programs in stem cell biology involving collaborative efforts of the laboratories of Dr. Peter Oettgen and Dr. Rosenzweig. These include a range of activities from fundamental research aimed at understanding signals controlling embryonic stem cell differentiation to translational studies using tissue engineering to repair injured hearts in animal models as well as studies of circulating stem cells in BIDMC patients with coronary disease, who are recruited in collaboration with our interventional cardiologists. These studies are being combined with genetic analyses in an effort to understand the mechanistic basis and clinical implications of results obtained through genome-wide association studies.

Newly recruited faculty members bring exciting research directions to the BIDMC Cardiovascular program. Takashi Matsui, MD, PhD, and Maria Kontaridis, PhD, have independent programs that focus on signaling mechanisms in cardiac function and heart failure, an area in which there is a growing clinical need for novel therapeutic targets. Dr. Matsui's laboratory has recently identified a pathway that, in animal models, protects against functional deterioration after a heart attack. Understanding the mechanism(s) behind this exciting observation and exploring its implications for clinical care are major focal points of his research program. Dr. Kontaridis's work has provided important insights into the role of the Shp-2 phos-

phatase in congenital cardiac syndromes that involve the heart and valves. Zolt Arany, MD, PhD, brings expertise in cardiac metabolism. Alterations in cardiac metabolism are thought to play an important role in heart failure, as well as contributing to the cardiac complications seen from the growing epidemic of metabolic diseases, such as diabetes. Interestingly, Dr. Arany has also recently identified a novel pathway controlling growth of new blood vessels (angiogenesis) and this discovery is likely to have implications not only in cardiovascular disease but also in other settings, such as cancer.

Federica del Monte, MD, PhD, has made seminal observations documenting the importance of sarcoplasmic calcium handling in heart failure which have laid the foundation for two ongoing clinical gene therapy trials. More recently, Dr. del Monte has discovered that protein “misfolding” – akin to what happens in brains affected by Alzheimer’s disease – may also play a role in heart failure – perhaps contributing to the close connection between heart failure and aging. Dr. del Monte is also in the process of establishing a Cardiovascular Core Laboratory providing pre-clinical animal models of cardiovascular disease to enable investiga-

tors to test therapeutic strategies involving novel devices or medicines. Finally, Heather Duffy, PhD, a recent recruit from Columbia, has established a successful program examining mechanisms of infarction-related ventricular arrhythmia. Her recruitment provides an opportunity to complement our world-class clinical electrophysiology program with outstanding basic and translational science.

● *Awards and Honors*

ShiYin Foo, PhD won the 2008 GlaxoSmithKline International Young Investigator’s award. Eli Gelfand, MD received the Faculty Development Award (administered by Stafford I. Cohen, MD). Yuchi Han, MD won the ACCF/GE Cardiovascular Imaging Career Development Award for 2008-2010. Mark E. Josephson, MD was presented with the prestigious American College of Cardiology “Gifted Teacher Award” for his many years as an exemplary role model and outstanding teacher of medical students, residents, fellows and physicians both nationally and internationally. David T. O’Halloran, MD was awarded the BIDMC First Year Fellows’ Teaching Award.

● *Faculty*

Evan Appelbaum, MD	Ernest Gervino, ScD	Roger J. Laham, MD	David O’Halloran, MD
Zoltan Arany, MD, PhD	C. Michael Gibson, MD, MS	David E. Leeman, MD	Panos Papageorgiou, MD, PhD
Julian M. Aroesty, MD	Ary L. Goldberger, MD	Stanley M. Lewis, MD	Dana C. Peters, PhD
Joseph P. Carrozza, MD	Aparna Gosavi, MD	Jian Li, PhD	Duane S. Pinto, MD
James D. Chang, MD	Thomas Hauser, MD, MMSc	William H. Maisel, MD, MPH	Carl A.F. Rasmussen, MD, PhD
Stafford I. Cohen, MD	Yuchi Han, MD	Warren J. Manning, MD	Matthew R. Reynolds, MD, MSc
Donald E. Cutlip, MD	Robert W. Healy, MD	John E. Markis, MD	Anthony Rosenzweig, MD
Regis A. de Silva, MD	Kalon K.L. Ho, MD, MSc	Takashi Matsui, MD, PhD	Samuel J. Shubrooks, Jr, MD
Federica del Monte, MD, PhD	Francis E. Hubbard, MD	Michael G. McLaughlin, MD	Richard L. Verrier, PhD
Heather S. Duffy, PhD	Mark E. Josephson, MD	Murray A. Mittleman, MD, DrPH	Francine K. Welty, MD, PhD
Loryn S. Feinberg, MD	Peter M. Kang, MD	Reza Nezafat, PhD	Susan B. Yeon, MD, JD
Lawrence A. Garcia, MD	Joseph P. Kannam, MD	J. Peter Oettgen, MD	Peter J. Zimetbaum, MD
Eli V. Gelfand, MD	Benet S. Kolman, MD		
	Maria Kontaridis, PhD		

## ● Selected Publications

Arany Z, Foo SY, Ma Y, Ruas JL, Bommi-Reddy A, Girnun G, Cooper M, Laznik D, Chinsomboon J, Rangwala SM, Baek KH, Rosenzweig A, Spiegelman BM. HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1 $\alpha$ . *Nature* 2008; 451:1008-12.

Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; 356:1020-9.

Gibson CM, Pride YB, Buros JL, Lord E, Shui A, Murphy SA, Pinto DS, Zimetbaum PJ, Sabatine MS, Cannon CP, Josephson ME. Association of impaired thrombolysis in myocardial infarction myocardial perfusion grade with ventricular tachycardia and ventricular fibrillation following fibrinolytic therapy for ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2008; 51:546-51.

Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Ansel G, Strickman NE, Wang H, Cohen SA, Massaro JM, Cutlip DE. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008; 358:1572-9.

Maisel WH, Kramer DB. Implantable cardioverter-defibrillator lead performance. *Circulation* 2008; 117:2721-3.

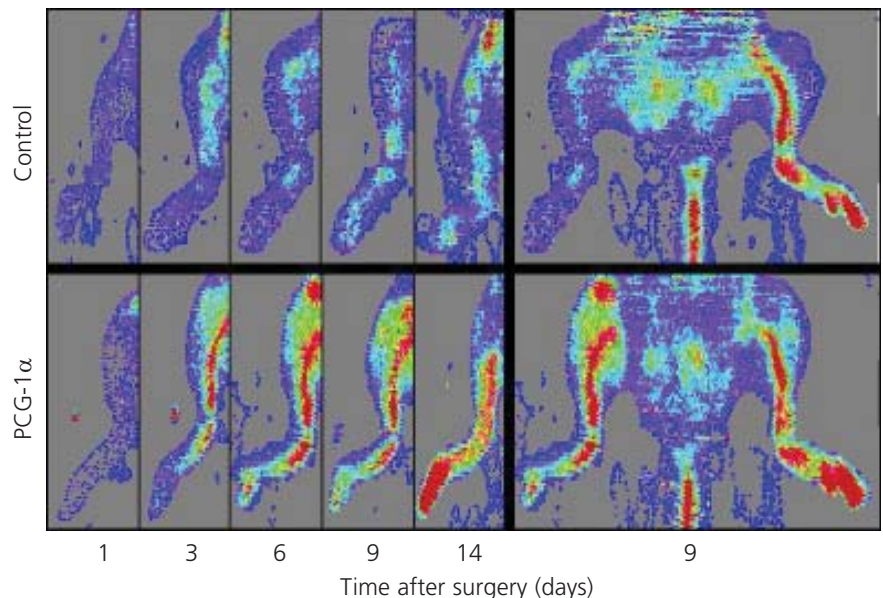
Peters DC, Wylie JV, Hauser TH, Kissinger KV, Botnar RM, Essebag V, Josephson ME, Manning WJ. Detection of pulmonary vein and left atrial scar after catheter ablation with three-dimensional navigator-gated delayed enhancement MR imaging: initial experience. *Radiology* 2007; 243:690-5.

Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, Kralovec S, Sediva L, Ruskin JN, Josephson ME. Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med* 2007; 357:2657-65.

Rosenzweig A. Scanning the genome for coronary risk. *N Engl J Med* 2007; 357:497-9.

Wylie JV, Jr., Peters DC, Essebag V, Manning WJ, Josephson ME, Hauser TH. Left atrial function and scar after catheter ablation of atrial fibrillation. *Heart Rhythm* 2008; 5:656-62.

Yeon SB, Sabir A, Clouse M, Martinezclark PO, Peters DC, Hauser TH, Gibson CM, Nezafat R, Maintz D, Manning WJ, Botnar RM. Delayed-enhancement cardiovascular magnetic resonance coronary artery wall imaging: comparison with multislice computed tomography and quantitative coronary angiography. *J Am Coll Cardiol* 2007; 50:441-7.



- PGC-1 $\alpha$  accelerates recovery in a mouse model of limb ischemia. Mice that transgenically express PGC-1 $\alpha$  in skeletal muscle (TG), and wildtype controls (WT), underwent surgical ligation of the femoral artery on day 0. This procedure stops nearly all flow to the leg, as shown by infrared scanning (left-most panels: blue = low flow, red = high flow). Recovery of blood flow was then followed over the subsequent 14 days. Mice expressing PGC-1 $\alpha$  (bottom panels) recovered blood flow faster than normal controls (top panels). From Arany et al. *Nature* 2008.